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Evaluation of the Effect of Combination Therapy on Treatment of COVID-19: A Cohort Study

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Abstract

Background: COVID-19 is a new disease for which a definitive treatment has not yet been proposed.
Objectives: The present study aimed to investigate the effect of combination therapy on the treatment of COVID-19 due to the importance of finding an appropriate treatment for this epidemic disease.
Methods: This two-center cohort study included 175 confirmed COVID-19 inpatients at two medical centers designated for the treatment of COVID-19 patients in Qom and Qazvin, Iran. In this study, four different groups of drug regimens were studied which included G1 (azithromycin, prednisolone, and naproxen), G2 (lopinavir/ritonavir, azithromycin, naproxen, and prednisolone), G3 (hydroxychloroquine, azithromycin, naproxen, and prednisolone), and G4 (levofloxacin, vancomycin, hydroxychloroquine, and oseltamivir). It should be noted that G1, G2, G3, and G4 treatment regimens were used on 48, 39,30, and 77 patients, respectively.
Results: The study participants included 175 confirmed COVID-19 patients with mean±SD age of 58.9 ±15.1 years, out of whom 80 (46%) patients were male and the rest were females. The results indicated that the hospital stay period was significantly shorter in the G1 compared to other groups (G1:5.9±2.4, G2:8.1±4.2, G3: 6.3±1.7, and G4: 6.4±2.9; [P-value=0.008]). It should be noted that pulse rate, oxygen saturation, hemoglobin, and platelet count (PLT) changed significantly during the study in four treatment groups; however, a significant change in temperature, creatinine, and white blood cell (WBC) was observed only in G3, G4, and G1 groups, respectively. The number of ICU admissions and deaths were not statistically significant among the patients who received the four treatment regimens (P=0.785). Based on the results, the history of ischemic heart disease, baseline oxygen saturation, WBC, neutrophil, lymphocyte count, and C-reactive protein (CRP) are the risk factors for the prolonged hospital stay in COVID-19 patients.
Conclusion: The obtained results in this study indicated that the combination of azithromycin, prednisolone, and naproxen is the most effective regimen for the treatment of COVID-19, compared to three other combination treatment regimens.

Keywords: Anti-inflammatory drugs, Antiviral drugs, Combination therapy, Corticosteroid, COVID-19, Immunomodulators drugs

1. Background

Coronavirus disease 2019 (COVID-19) is a new virus disease that started in Wuhan, China, and was quickly transformed into a pandemic. This pandemic has posed an unprecedented impact on the healthcare system due to the high spread of the disease and its mortality rate (1).

Nowadays, the lack of a specific, effective, and proven standard treatment for COVID-19 disease is one of the serious public health challenges worldwide. Many aspects of COVID-19 disease including demographic characteristics of patients, clinical features, and biological abnormalities, as well as the radiological and pathological patterns of the disease have been described so far. Moreover, many studies have addressed different therapeutic strategies for the management of the disease.

The proposed medicines for the treatment of COVID-19 included Kaletra (lopinavir–ritonavir), remdesivir, oseltamivir, ribavirin, sofosbuvir (2-5), immunomodulators, such as chlorine and hydroxychloride (6-7) as well as anti-inflammatory medications, such as corticosteroids (8-10) or their combination (11).

The main COVID-19 management strategy has its focus on antiviral treatments with Kaletra (lopinavir–ritonavir), remdesivir, oseltamivir, ribavirin, sofosbuvir (2-5), immunomodulators, such as chlorine and hydroxychloride (6,7) and anti-inflammatory

therapies, such as corticosteroids (8-10) or their combination, owing to the two-phase pathogenesis of the disease (11).

Antiviral therapies are effective in the treatment of such diseases as Middle East respiratory syndrome coronavirus, severe acute respiratory syndrome coronavirus, and influenza. However, the effectiveness of these medications in the treatment of COVID-19 has not been widely approved, even though evidence indicates the decreasing pattern of viral load over time. The other management strategies are focused on anti-inflammatory therapies, such as the use of corticosteroids, particularly in patients with organizing pneumonia patterns (8,9).

In general, the administration of corticosteroids has been recommended for critically ill patients suffering from COVID-19 (10). A combination of antiviral drugs with corticosteroids has also been suggested which may effectively decrease viral load and treat inflammation in the patients.

2. Objectives

Due to the importance of COVID-19 treatment, the present study aimed to investigate the combination therapy on the treatment of this disease.

3. Methods

This cohort study included 175 confirmed COVID-19 patients in the age range of 25-95 years who were hospitalized at two medical centers designated for the treatment of COVID-19 in Qom and Qazvin, Iran, from March 17 to April 29, 2020. All the COVID-19 patients in this study were diagnosed according to the WHO interim guidelines. The medical records of all patients were obtained from the hospital data and the death of any patient was recorded as an outcome. The study was approved by the Medical Ethics Committee of Baqiyatallah University of Medical Sciences (IR.BMSU.REC.1399.001).

According to the data obtained from the hospitals, each patient received one of the four combination therapy regimens and was consequently assigned to one of the four groups of 1, 2, 3, and 4. Medicines applied on patients in Group1 included azithromycin (250 mg daily), prednisolone (25 mg/daily), and naproxen (250 mg BD). Medication in Group 2 included lopinavir/ritonavir (200/50 mg tablets two times/12 h), azithromycin (250 mg daily), naproxen (250 mg BD), and prednisolone (25 mg daily). Patients in Group 3 took hydroxychloroquine (250 mg tablets two times/12 h), azithromycin (250 mg daily), naproxen (250 mg BD), and prednisolone (25 mg daily). Medicine regimen in Group 4 consisted of meropenem (1gr/8h), levofloxacin (500 mg/day), vancomycin (1gr/12h), hydroxychloroquine (200 mg/12 h), and oseltamivir (75 mg/12 h).

Inclusion criteria in this study included 1) Diagnosis of COVID-19 based on approved diagnostic tools, such as real-time RT-PCR (throat-swab specimens) or chest CT scan according to the WHO interim guidelines which included symptoms of typical coronavirus pneumonia (i.e., patchy infiltration and focal unilateral to ground-glass opacity, ill-defined margins, smooth or irregular interlobular septal thickening, air bronchogram, crazy-paving pattern, and thickening of the adjacent pleura) (23-14), 2) Oxygen saturation (SPO2) ≤93, 3-16≤Age≤100, 3) Patients with controlled diabetic status, no history of gastrointestinal bleeding, non-pregnant and non-lactating mothers, 4) Patients with no history of immunosuppressive therapy or chemotherapy in the past month. However, patients with high missing data in the medical records were excluded from the study.

In this study, the patients' demographic data, history of past diseases, and laboratory findings (i.e., white blood cell count (WBC), neutrophil, lymphocyte, hemoglobin, platelet count (Plate), C-reactive protein (CRP), creatinine) were obtained. Moreover, the vital signs of the patients were monitored which included temperature, respiratory rate (RR), pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and resting stable oxygen saturation (5 min after disconnecting). Eventually, symptoms, such as cough, fever, dyspnea, weakness and lethargy, headache, dizziness, anorexia, and body pains were extracted from the medical records of hospitalized patients.

3.1. Statistical Analysis

The data were analyzed using R software (version 3.2 for Windows) based on non-missing values through the Kruskal-Wallis Test, analysis of variance (ANOVA), analysis of covariance (ANCOVA), and Chi-square test (for comparing demographic and baseline variables among the four combination regimens). Qualitative and quantitative variables were reported in percentages and mean±SD, respectively. A p-value less than 0.05 (P≤0.05) was considered statistically significant.

4. Results

Initially, the medical records of 490 patients were randomly selected out of 1270 hospitalized patients. Eventually, the medical records of 175 patients were analyzed (Figure 1).

Females (n=95, 54%) constitutes the majority of COVID-19 patients (n=175) in this study. The mean±SD age of patients was estimated at 58.94±15.14 years with the age range of 25–95 years. Table 1 presents the distribution of demographic characteristics, baseline variables, comorbidities, clinical features, and laboratory findings of four treatment groups. The major comorbidities at the time of admission included

hypertension (27%), ischemic heart disease (9%), and hypothyroidism (5%). No significant difference was observed in variables of four treatment groups except for variations in gender (P<0.001), body temperature (P=0.001), CRP (P=0.038), and pulse rate (P= 0.015).

Table 2 presents the distribution of discharge status and hospital stay in four treatment groups. The number of ICU admissions and deaths were not found to be statistically significant in the four treatment groups (P=0.785). In addition, hospital stay was found to be significantly lower in Group1 compared to other groups (P=0.008; Table 2). The hospital stay was just about two days shorter in Group1, compared to Group 2, and 0.5 days shorter than that in Group 3 and 4.

As can be seen in Table 3, PR, oxygen saturation, hemoglobin, and PLT have significantly changed during the study in four treatment groups; however, temperature, creatinine, and WBC significantly changed in Group 3, 4, and 1, respectively.

The history of ischemic heart disease was more prevalent among the patients discharged from ICU (n=11) and those who died (n=8) in this study (9% vs 26%, P-value=0.026). Based on the results, baseline SPO2 (88.1±6.78 vs. 84.87±7.4), WBC (7.41±9.09 vs. 13.03±14.2, P=0.013), neutrophil (72.36±12.7 vs. 80.23±6.64, P-value=0.022), lymphocyte count (16.18±6.04 vs. 16.18±6.04, P-value=0.038), and CRP (21.65±17.26 vs. 29.11±12.8, P-value=0.022) were the risk factors for the prolonged hospital stay of COVID-19 patients.

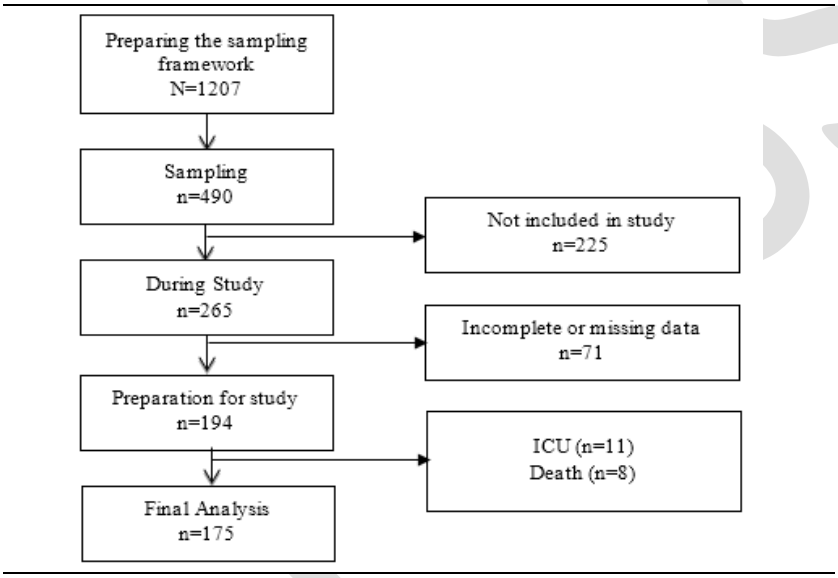

Figure 1. Study diagram of four treatment groups

Table 1 . The distribution of demographic and clinical characteristics, comorbidity, and laboratory finding of four treatment groups

Variable	Regimen				Total (n=175)	P-value
	G1(N=44)	G2(N=37)	G3(N=27)	G4(N=67)		
Gender (Male)	18(41%)	7(19%)	15(56%)	40(60%)	80(46%)	0.001
Smoking (yes)	2(4%)	0(0%)	2(7%)	2(3%)	6(3%)	0.442
Age	57.1(±16.7)	61.7(±14.7)	57.9(±14.5)	59.4(±14.6)	58.9(±15.1)	0.603
BMI	29.5(±4.9)	27.8(±5.1)	29.3(±8.1)	26.9(±3.9)	28.2(±5.4)	0.068
Hypertension (yes)	10(%23)	6(%16)	10(%37)	21(%31)	47(%27)	0.201
Diabetes mellitus (yes)	11(%25)	5(%14)	7(%26)	17(%25)	40(%23)	0.507
Hypothyroidism (yes)	1(%2)	1(%3)	4(%15)	2(%3)	8(%5)	0.052
IHD (yes)	1(%2)	4(%11)	3(%11)	7(%10)	15(%9)	0.316
CABG (yes)	0(%0)	0(%0)	0(%0)	3(%4)	3(%2)	0.178
HLP (yes)	2(%5)	1(%3)	0(%0)	2(%3)	5(%3)	0.740
SpO2	89.9(±7.9)	86.7(±7.6)	87(±5.1)	87.9(±6)	88.1(±6.8)	0.184
Temperature	36.9(±0.8)	37.3(±0.9)	36.7(±0.3)	36.7(±0.8)	36.88(±0.80)	0.001
SBP	123.7(±15.8)	118.3(±13)	124.7(±18.8)	121(±18.6)	121.6(±16.9)	0.389
DBP	75.7(±10.6)	76.6(±10)	78(±14.1)	76.1(±12.6)	76.4(±11.77)	0.879
PR	92.5(±17.1)	94.5(±17.5)	85.7(±13.7)	85.3(±15.8)	89.11(±16.6)	0.015
RR	18.6(±3.5)	18.1(±2.4)	18.2(±2.2)	18.8(±2.7)	18.53(±2.81)	0.613
WBC	10.9(± 19.2)	5.7(±2.6)	6.2(±2.7)	7.1(±3.5)	7.4(±9.1)	0.089
Neutrophil	73.3(±1.1)	71(±12.2)	73.6(±12.3)	71.9(±14.3)	72.4(±12.7)	0.841
Lymphocytecount	20.7(±9.3)	20.7(±9.3)	20.7(±9.3)	20.7(±9.3)	21.9(±10.7)	0.530
Hemoglobin	13.7(±1.9)	13.4(±1.7)	14(±1.3)	13.7(±1.9)	13.7(±1.8)	0.647
PLT	216.3(±73.5)	191.5(±55)	176.6(±52.2)	196.6(±94.4)	197.1(±76.9)	0.198
CRP	14.8(±12.7)	24.3(±26.9)	26.6(±13.4)	22.4(±15.3)	21.6(±17.3)	0.038
CR	1.3(±0.8)	1(±0.4)	1.1(±0.4)	1.3(±0.8)	1.2(±0.7)	0.140

Table 2 .The distribution of discharge status and hospital stay in four treatment groups

Post-treatment	Group				P-value
	G1(N=48)	G2(N=39)	G3(N=30)	G4(N=77)	
Discharge Status					
Discharge	44(%92)	37(%95)	27(%90)	67(%87)	0.785
ICU	3(%6)	1(%2.5)	1(%3)	6(%8)	
Death	1(%2)	1(%2.5)	2(%7)	4(%5)	
	G1(N=44)	G2(N=37)	G3(N=27)	G4(N=67)	P-value
Hospital Stay	5.9(±2.4)	8.1(±4.2)	6.3(±1.7)	6.4(±2.9)	0.008

Table 3. The mean±SD of laboratory and vital sign variables at the time of hospitalization and discharge in four treatment groups

Variables	Group	Hospitalization	Discharge	P-value	P-value
		Mean(±SD)	Mean(±SD)	Within	Between
Hemoglobin	G1	13.69(±1.94)	12.41(±2.15)	<0.001	0.527
	G2	13.43(±1.68)	10.57(±1.7)	0.018	
	G3	14.03(±1.34)	13.44(±1.83)	0.011	
	G4	13.72(±1.93)	13.16(±2.33)	0.003	
PLT	G1	209.24(±73.76)	252.56(±85.18)	0.002	0.022
	G2	189.73(±55.3)	253(±98.17)	0.001	
	G3	180.9(±55.53)	207.3(±72.94)	0.01	
	G4	195.83(±92.12)	222.32(±100.44)	0.04	
CRP	G1	14.83(±12.67)	12.15(±10.83)	0.348	0.275
	G2	24.31(±26.86)	20.54(±7.72)	0.225	
	G3	26.56(±13.41)	26.43(±15.45)	0.845	
	G4	22.38(±15.31)	27.93(±14.53)	0.258	
Creatinine	G1	1.34(±0.8)	1.39(±0.84)	0.309	0.829
	G2	0.97(±0.41)	0.8(±0.14)	0.157	
	G3	1.14(±0.35)	0.96(±0.19)	0.022	
	G4	1.25(±0.8)	1.15(±0.48)	0.009	
WBC	G1	10.91(±19.22)	19.04(±34.82)	0.032	0.008
	G2	5.73(±2.62)	6.7(±1.04)	0.109	
	G3	6.24(±2.66)	6.37(±2.3)	0.936	
	G4	7.12(±3.51)	6.13(±1.77)	0.083	
Neutrophil	G1	73.29(±11.1)	71.17(±13.22)	0.077	0.433
	G2	70.96(±12.24)	71.2(±13.2)	0.881	
	G3	73.56(±12.28)	71.17(±12.89)	0.353	
	G4	71.85(±14.27)	72.76(±11.25)	0.469	
Lymphocyte	G1	20.68(±9.34)	21.22(±11.7)	0.904	0.245
	G2	23.49(±10.11)	12.5(±4.1)	0.180	
	G3	20.07(±9.3)	23.44(±10.46)	0.343	
	G4	22.45(±12.3)	22.5(±11.52)	0.173	
SpO2	G1	89.89(±7.94)	93.17(±3.69)	0.004	0.131
	G2	86.72(±7.57)	88.86(±17.92)	0.001	
	G3	86.96(±5.13)	90.39(±3.05)	<0.001	
	G4	87.89(±6.01)	90.81(±4.95)	0.001	
Temperature	G1	36.88(±0.79)	36.64(±0.41)	0.029	0.014
	G2	37.31(±0.91)	36.75(±0.4)	0.039	
	G3	36.68(±0.35)	36.57(±0.4)	0.155	
	G4	36.71(±0.8)	36.63(±0.6)	0.355	
SBP	G1	123.66(±15.8)	120.85(±11.9)	0.580	0.468
	G2	118.32(±12.97)	121.33(±12.46)	0.410	
	G3	124.7(±18.82)	122.08(±11.97)	0.757	
	G4	121(±18.63)	118.84(±15.83)	0.241	
DBP	G1	75.68(±10.61)	77.88(±8.28)	0.120	0.128
	G2	76.59(±10)	74.38(±7.27)	0.944	
	G3	77.96(±14.08)	80.17(±7.48)	0.430	
	G4	76.13(±12.6)	74.4(±10.55)	0.166	
PR	G1	92.52(±17.09)	81.81(±10.86)	0.002	0.479
	G2	94.54(±17.47)	82.94(±13.93)	0.05	
	G3	85.7(±13.75)	78.79(±12.32)	0.028	
	G4	85.28(±15.79)	80.6(±11.28)	0.054	
RR	G1	18.64(±3.51)	18.41(±1.78)	0.744	0.323
	G2	18.14(±2.39)	17.07(±1.79)	0.153	
	G3	18.19(±2.22)	18.35(±3.97)	0.493	
	G4	18.83(±2.73)	18.72(±2)	0.945	

5. Discussion

The COVID-19 pandemic has had a notable impact on the death rate of the health system and inflicted huge socio-economic costs on numerous countries around the world over the past year (15). The lack of a clear, reliable, and proven standard therapy for COVID-19 is one of the serious public health

problems. Therefore, the current research aimed to evaluate the effect of combination therapy on the treatment of COVID-19 disease. Based on the obtained result in this study, the combination of azithromycin, prednisolone, and naproxen led to better clinical results, compared to the other three combination therapy regimens. This result can be attributed to the concurrent use of azithromycin and prednisolone. Moreover, an early upper respiratory tract shedding of the virus has been confirmed in asymptomatic and pauci symptomatic patients at the early emergence of the symptoms (16). Therefore, antiviral regimens and handling of virus load lost effect in symptomatic patients over time, considering the fact that patients in this study were not in the early phase of the disease. Moreover, anti-inflammatory drugs have been recommended for the treatment of pulmonary lesions and improvement of clinical outcomes in some patients due to their effectiveness in controlling cytokine storms (17).

The results of a study conducted by Russell indicated that low-dose prednisolone could have beneficial effects on the treatment of COVID-19 (18). Another study performed by Arshad et al. showed that the application of azithromycin was associated with a reduction in mortality rate associated with COVID-19 (19). In addition, a review study conducted by Jean et al. reported the excellent clinical efficacy of hydroxychloroquine along with azithromycin on COVID-19 patients (20). The pharmacological mechanism of azithromycin and prednisolone in the treatment of COVID-19 is presented in the studies conducted by Sultana et al. (21) and Caruso et al., respectively (22). Based on the results of a study conducted by Vahedi et al. low-dose prednisolone in combination with azithromycin, naproxen, and lopinavir/ritonavir led to a reduction in COVID-19 hospital stay (11). Based on the results of a meta-analysis conducted by Sarma et al. (23) no significant improvement was observed in the status of COVID-19 patients treated with hydroxychloroquine. In addition, the results of a review study by Yousefi et al. indicated that neuraminidase inhibitors, such as oseltamivir, peramivir, and zanamivir were not recommended for the treatment of COVID-19 disease (24).

The results of another study showed that laboratory variables, such as WBC, lymphocyte, CRP, as well as SPO2 were associated with a hospital mortality rate (25).

Regarding the limitations of the present study, one can refer to the lack of certain clinical recording and laboratory results, which was due to inadequate patient profiles in the hospitals' electronic medical reports. Consequently, the recommendations in this study were made based on the available data.

6. Conclusion

Based on the obtained result in this study, the combination of azithromycin, prednisolone, and naproxen was a more effective treatment regimen, compared to the other three combination therapy regimens.

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Footnotes

Authors' contribution: Amir Hosein Ghazale, Ali Ghazvini and Mostafa Ghanei conducted the study design. Data collection was performed by Ensieh Vahedi, Shideh Omidian, Abolfazl Mozafari, Mohammad Rezapour, Nafiseh Rastgoo, Fatemeh Movaseghi, Fateme Mansouri, Mohammad Ali Zohal, Maryam Gheraati, Hassan Goodarzi, Amir Mohammad Dehghan Banadkooki, Amir Mohammad Dehghan Banadkooki, Shahrzad Saloo, and Hesamodin Salou. Data analysis was carried out by Mohammad Gholami Fesharaki. Eventually, Mohammad Gholami Fesharaki, Mostafa Ghanei, and Amir Hosein Ghazale wrote the manuscript.

Ethical Approval: The cohort study was approved by the Medical Ethics Committee of Baqiyatallah University of Medical Sciences (IR.BMSU.REC. 1399.001) and was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Conflict of interests: The authors declare that he has no conflicts of interest regarding the publication of the present study.

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Informed consent: Informed consent was not required to conduct this study.

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